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Strengthening Bioterrorism Prevention: Global Biological Materials Management

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The anthrax attacks of 2001 demonstrated that bioterrorism poses a significant threat to U.S. national security. This threat is increasing as a result of the rapid expansion in scale and technical capabilities of the global biotechnology industry, which is broadening the availability of materials, technologies, and expertise needed to produce a biological weapon and is lowering the barriers to biological weapons terrorism and proliferation. At the same time, there has been a rise of sophisticated yet loosely networked transnational terrorist groups that have shown an interest in bioterrorism. The United States must confront this convergence. Although the U.S. government pursues many different biodefense programs to bolster its ability to detect and respond to a bioterrorist attack, these efforts must be augmented with preventive measures to meet today's international challenges. U.S. Homeland Security Presidential Directive 10 of April 2004 defines "Prevention and Protection" as one of the four essential pillars of the U.S. response to the bioterrorist threat. However, while bioscience and policy experts have proposed a variety of preventive initiatives, the creation of such programs has been slow and limited. Global biological materials management, which would focus on identifying and protecting those biological materials at the greatest risk of being used maliciously, is one potential solution. Such an approach would augment current U.S. biodefense efforts, provide the international community an effective means of mitigating the global threat of bioterrorism, and strengthen the international community's battle against emerging infectious disease.

The threat of biological weapons (BW) proliferation and terrorism is evolving, largely as a result of rapid advances in biotechnology and the dramatic expansion of public and private bioscience worldwide. While these trends offer tremendous opportunities for improving human health and well-being, they also increase the risk that bioscience could be exploited by someone intent on causing harm. Experts suggest that the risk of bioterrorism will increase as the technology advances and becomes more widespread and as the costs of and technical impediments to creating a biological weapon continue to decline. They predict that, over time, terrorists will resort to bioterrorism instead of attacks with conventional explosives and that bioterrorism may produce greater consequences than are possible today.[1–5]

According to a 2004 report of the National Intelligence Council:

> The most worrisome trend has been an intensified search by some terrorist groups to obtain weapons of mass destruction. Our greatest concern is that these groups might acquire biological agents or, less likely,

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> a nuclear device, either of which could cause mass casualties. . . . Terrorist use of biological agents is therefore likely, and the range of options will grow.[6]

A 2005 report by the Commission on the Intelligence Capabilities of the United States Regarding Weapons of Mass Destruction asserted that "in the near future, the biotechnology revolution will make even more potent and sophisticated weapons available to small or relatively unsophisticated groups."[7]

Today, there is a real danger that terrorists could acquire the necessary means from the legitimate bioscience sector to perpetrate bioterrorism. Scientists with the expertise necessary to misuse biology can be found internationally in nearly all areas of the life sciences. Important advances in the biosciences, many of which could be exploited to cause harm, are published almost every day in scientific journals, research publications, patents, and on the internet. Modern biotechnology, including the tools necessary to develop and disseminate a low-grade biological weapon, is also ubiquitous in the international pharmaceutical, agricultural, and microbiological communities. And viable and virulent organisms—almost all of which occur naturally—are stored and used in legitimate bioscience facilities around the globe. The fundamentally "dual-use" nature of all the technical building blocks of biological weapons—materials, technology, and expertise—not only provide ample opportunities for terrorists to exploit but also make imposing controls extremely difficult.

Moreover, it is noteworthy that many terrorist organizations are active in those parts of the world that are experiencing both rapidly expanding biotechnology and frequent outbreaks of highly infectious disease. In other words, the increasing availability of dual-use materials, technology, and expertise in certain regions may facilitate terrorist efforts to acquire, develop, and disseminate a biological agent. Some of these terrorist groups are highly independent and have demonstrated a willingness to experiment with various destructive technologies. Some also possess significant financial resources, which would enable them to purchase sophisticated laboratory equipment, recruit or bribe well-trained scientists and engineers, and acquire dangerous pathogens.

These trends are significant and compel the United States to create programs that counter the evolving global threat of bioterrorism. In response to the anthrax attacks of 2001, the U.S. government dramatically expanded the nation's domestic biodefense programs, which aim to improve the ability of the U.S. to *detect and respond to* the next bioterrorist attack. These activities include the development and stockpiling of medical countermeasures, improving sensor and detection capabilities, and bolstering the U.S. public and agricultural health infrastructure.

However, the United States also must develop programs that are specifically designed to *prevent* use of biological weapons by terrorists, and this can be accomplished by limiting opportunities for such individuals or groups to exploit legitimate bioscience. Such preventive programs fall within the realm of what historically has been called "biological weapons nonproliferation" (BWNP)—an effort to curb the development, spread, and use of biological weapons.

Yet the kinds of preventive programs needed today to counter the threat of bioterrorism are fundamentally different from those that have been implemented in the past. Traditionally, BWNP has focused on the threat of state-sponsored proliferation in weapons—not terrorism—and has emphasized dismantlement and destruction of former state-owned weapon facilities. New biological threat reduction programs should focus on counterterrorism and emphasize engagement with the legitimate bioscience community.

U.S. policymakers have already voiced the need to invest in new biological threat reduction programs. The promulgation in April 2004 of Homeland Security Presidential Directive 10 (HSPD-10),* *Biodefense for the 21st Century*, affirmed the government's commitment to combating the threat of bioterrorism and articulated a growing imperative for international threat reduction. The directive defines "Prevention and Protection" as one of the four essential pillars of the U.S. response to the bioterrorist threat:

> Preventing biological weapons attacks is by far the most effective approach to biodefense. Prevention requires the continuation and expansion of multilateral initiatives to limit the access of agents, technology, and know-how to countries, groups, or individuals seeking to develop, produce, and use these agents.[8]

The international community has also begun to recognize the need to develop preventive solutions to counter the contemporary bioterrorist threat. United Nations Security Council Resolution 1540 urges nations to take preventive measures to mitigate the threat of biological, chemical, and nuclear terrorism.[9] The International Committee of the Red Cross (ICRC), the International Criminal Police Organization (Interpol), and the Organization for Economic Cooperation and Development (OECD) have recently launched initiatives to prevent the malicious use of pathogens and toxins.[10–12]

The U.S. scientific community has acknowledged the national security challenges that the expanding biotechnology industry is creating. As a result of a National Academy of Sciences report in 2003,[1] the U.S. established the National Science Advisory Board for Biosecurity (NSABB) and has given it responsibility for considering bioscience codes of

*Also known as National Security Presidential Directive 33 (NSPD-33).

conduct and developing a system of institutional and federal review of bioscience research.[13] In 2006, a National Academy of Sciences report concluded that the broad spectrum of biological threats will expand in the future and implored the "global community of life scientists to adopt a common culture of awareness and a shared sense of responsibility" to mitigate these security concerns.[14]

Although these policy directives and analyses identify the problem and offer many valuable general recommendations, none presents a clear method for reducing the risks associated with the expanding global biotechnology industry. In many ways, this is not surprising: The problem is so complex that searching for a single panacea is probably foolhardy. Instead, the U.S. and the international community will need to simultaneously apply many different solutions—in varying degrees, depending on the situation—to mitigate the advancing threat of bioterrorism and BW proliferation.

We accept the current priority of U.S. policy to strengthen our ability to detect and respond to a catastrophic bioterrorist incident. However, we believe that a comprehensive biodefense program must include not only *preparedness* but also *prevention*. Regrettably, the field of bioterrorism prevention is currently not well defined or well executed internationally. This article proposes a focus on controlling high-risk biological materials globally. Such a "global biological materials management" approach is one way to engage the legitimate international bioscience community and build international bioscience collaborations that focus on the safe, secure, and responsible use of dangerous pathogens. This program could not only make it more difficult for groups and individuals to perpetrate bioterrorism, but it could also strengthen the international community's ability to combat emerging infectious disease.

Challenges to Developing New Preventive Programs

Experts in the bioscience and policy communities have suggested various preventive measures to address the contemporary bioterrorist threat. Many cite the need to exercise some form of "responsible stewardship" over bioscience,[3] whether in the form of review of publications,[13] codes of conduct,[15] oversight of dangerous research,[16–21] international legally binding restrictions on access to pathogens,[22,23] or controls on equipment that could be used to build a biological weapon.[24]

However, developing new preventive programs to reduce the contemporary bioterrorist threat is a challenging endeavor. The legitimate international bioscience sector is immense and growing exponentially every year. Around the world, the economic opportunities offered by the rapidly evolving biomedical field have motivated governments to invest heavily in biotechnology. In addition to the widespread promulgation of biotechnology strategies and development plans, there has been a pronounced rise in the related infrastructure, especially high-containment biological research and diagnostic facilities. Consider Singapore, which less than a decade ago had no high-containment biological research facilities. Four years ago Singapore had three operational biosafety level three (BSL-3) facilities. And by this year, Singapore—an island country of just 4.3 million people—expects to have as many as 13 operational BSL-3 laboratories.[25] Singapore is not unique but simply a reflection of trends also evident in India, Thailand, and all over the world. Even Indonesia, a developing country with two operational BSL-3 laboratories, has plans for extensive infrastructure expansion: Next year the government plans to have as many as 10 BSL-3 laboratories in operation. With the international expansion of biotechnology and high-containment capacity comes an increase in the risk that it could be misused. So how can we protect what is seemingly ubiquitous?

The challenge is most acute in the area of biological information and expertise, which is globally distributed among thousands of bioscientists, research publications, journals, and patents. The progress of legitimate bioscience depends on the free flow of such information, making efforts to limit BW proliferation-related information often cumbersome and generally ineffective. Moreover, attempts at controlling biological information could jeopardize advances in basic science—advances that are fundamental to our ability to combat infectious disease.[26] While some experts have suggested regulating selected research areas of concern, any area of the biosciences could potentially be misused if an individual were intent on doing so. A wide variety of disciplines, all known for the development of beneficent applications—including microbiology, biophysics, meteorology, and sustainable agriculture—can contribute to the development and use of a biological weapon.

This dual-use problem also complicates efforts to develop a code of conduct. While it is valuable to encourage bioscientists to develop attitudes that shun BW proliferation and terrorism, such a vow remains contradictory: Many cutting-edge biological procedures and technologies with beneficent applications could also be used to advance BW proliferation and terrorism. Moreover, such an approach, while a prudent step in raising awareness among the legitimate scientific community, cannot deter terrorists committed to mounting a biological attack.

Challenges also exist to protecting the technologies and equipment that could be used to build and disseminate a biological weapon, especially in the international legal realm. These technologies are broadly distributed, making schemes to tag millions of pieces of dual-use equipment extremely impractical. While in theory it would be desirable

to control a narrow set of technologies that traditionally have been associated with large-scale production of biological weapons—large fermenters, aerosolization chambers, lyophilization equipment—the evolving state of the biosciences could make such efforts very resource intensive. Even if the international community could control this "specialized" equipment, terrorists need not rely on such technologies to successfully disseminate infectious disease. The development of biological weapons by "low-technology" approaches can be pursued on a small scale and in geographically distributed sites, allowing for easy relocation. Thus, identifying, let alone eliminating, clandestine bioterrorist operations will be very difficult for law enforcement.

Global Biological Materials Management: A Proposed Preventive Approach

Ultimately, it is unrealistic, cost-prohibitive, and counterproductive to try to manage all aspects of the emerging global biotechnology industry. In particular, we believe that attempts to control biological expertise, information, equipment, and technology would stymie the advance of science and harm the fight against infectious diseases. In contrast, we think that managing certain biological materials could provide important counter-bioterrorism benefits while also promoting scientific progress.

Many experts believe that biological weapons are most likely to be sought and used by terrorists, and that terrorists are likely to use readily available biological agents in laboratories, where they have been characterized and their viability and virulence established, as opposed to isolating agents from nature or pursuing the creation of novel pathogens.[7,27,28] Although almost every biological agent may be isolated from nature, this procedure can be technically difficult and the necessary skills are often much different from those required to culture a pathogen in the laboratory. Even if someone possesses the requisite skills, dangerous pathogens tend to be endemic to very specific environments and reservoirs.

For example, *Yersinia pestis*, the causative agent of plague, is often referred to as a biothreat agent distributed widely around the globe. Despite the presence of large numbers of endemic plague foci on all continents except Australia, together the foci cover only around 6–7% of the earth's land mass and cannot be considered widespread. Scattered throughout these foci are many different strains that exhibit tremendous genotypic and phenotypic diversity. In addition to genetic disparity in the bacterial genome, there is also extensive variation in plasmid content among strains. Consequently, strains differ widely in virulence potential, and it is still not well known what combination of genotypic and phenotypic traits are indicative of virulence in humans. Strains that are virulent to the natural reservoir—rodents—are not necessarily dangerous to people. As a result, successful isolation of bioweapon-suitable strains from nature, in a nonoutbreak situation, would be extremely challenging. An indication that dangerous strains may not be common in nature is that in 2003 only 182 deaths attributed to plague were reported worldwide, even though many of the foci overlap with large human populations.[29,30]

In theory, terrorists also have the option of constructing viable and virulent organisms synthetically or through genetic engineering of a relatively harmless agent. Yet today, the risk is relatively low that biological agents will be created by *de novo* synthesis or genetic engineering specifically for bioterrorism purposes. Terrorist groups would have to allocate extensive technical and financial resources for research on and characterization of a new organism. While it is possible to engineer a harmless agent to display heightened virulence, or to achieve antibiotic resistance in an existing agent, producing such a transformation is technically challenging, time-consuming, and costly. Besides its technical and financial demands, the synthesis of pathogens from scratch is far from tried and true and may result in decreased virulence or other undesirable characteristics. Thus far, the only study in which a mammalian pathogen has been synthesized *de novo* was in 2002, when Jeronimo Cello and colleagues synthesized the polio virus—a comparatively easy virus to synthesize and reconstitute. This synthetic virus was distinctly less lethal in mice than the natural polio virus.[19,20,31]

While the United States and the international community will need to find ways to address emerging issues such as *de novo* synthesis and super pathogens, the existence of the problem should not preclude the development of prioritized efforts to secure those natural biological materials in legitimate bioscience laboratories at the *greatest risk* of theft for use in bioterrorism. Moreover, not every bioscience facility houses collections of these high-risk pathogens and toxins. Only a small percentage of bioscience facilities around the world work with, characterize, and store those biological agents. Managing dangerous pathogens and toxins in those relatively few legitimate bioscience facilities around the globe—in a way that does not compromise critical research and diagnostics—is a viable bioterrorism prevention strategy.

A global biological materials management approach would also complement existing U.S. BWNP programs designed to counter state-based biological weapons proliferation. The U.S. continues to support the Biological Weapons Convention (BWC), which prohibits the production, stockpiling, acquisition, and use of biological weapons by Member States. By implementing global biological materials management programs, countries would strengthen their contribution to the BWC, which recently called for

the adoption of laboratory biosafety and biosecurity and improved disease surveillance to supplement the treaty. Such an approach would also complement the U.S. BWNP programs developed in the mid-1990s to engage the states of the Former Soviet Union. These programs, administered by the Departments of State and Defense, which initially focused on cooperative research as well as the dismantlement, destruction, legitimate reconstituting, and securing of former Soviet BW facilities, now include facility biosafety, pathogen security, and disease surveillance activities.[32–34]

A global biological materials management program should include the following technical components: (1) agent prioritization, (2) facility and transport biosafety and biosecurity, and (3) pathogen surveillance and outbreak control. All these activities will require extensive engagement and partnerships with the international community. In implementing such practices, policymakers and system designers must consider the unique operating environments within which protection measures need to be integrated, whether they are laboratories, commercial carriers, hospitals, or diagnostic facilities. Safety and security should be employed without jeopardizing legitimate research or compromising diagnostic and response practices that safeguard public and agricultural health. Attaining an appropriate balance among these considerations will be essential for achieving broad implementation.

At the same time, it is important to acknowledge the limitations of a global biological materials management approach. Reducing terrorist access to dangerous pathogens and toxins will not prevent bioterrorism or BW proliferation or even provide a guarantee that such agents could not be diverted from legitimate bioscience. However, global biological materials management programs can demonstrably improve the safety and security of dangerous pathogens and toxins worldwide—ultimately making it significantly more difficult for terrorists to steal or acquire these materials to use maliciously.

Agent Prioritization

Before embarking on an effort to protect biological materials worldwide, policymakers should identify *high-risk agents*: those pathogens and toxins that pose the greatest risk of being stolen and used as a bioterrorist weapon. Doing so will require detailed scientific analyses that evaluate the biochemical properties of a broad range of biological agents and that prioritize these pathogens and toxins according to their risk of malicious use.[35]

No comprehensive or widely accepted standard for biological agent prioritization has been publicly developed, either internationally or domestically. In the United States, 81 agents are regulated by the Select Agent Rule, but these agents are not secured or monitored according to the risk of bioterrorist use. Although the Select Agent Rule specifies that the security plan "must provide graded protection in accordance with the risk of the select agent or toxin," security requirements are not established for different levels of risk.[36] In other words, select agents *Y. pestis* (the causative agent of plague) and *Xylella fastidiosa* (the causative agent of Pierce's Disease, a lethal disease of grapevine)—the former widely known as a viable bioterror agent and the latter never considered as such—do not necessarily require different levels of protection. Several agent prioritization efforts have been initiated, but their scope is limited. The U.S. Centers for Disease Control and Prevention (CDC) began one such effort in 1999 and published the associated methodology in 2002.[37] Unfortunately, the methodology employed was not sufficiently transparent, and questions have been raised about the validity of numerous agents on the list.[38,39] Although this study is being revised, its usefulness to the international policy community may be compromised by its lack of a clear methodology and a graded prioritization scheme.

Admittedly, it is extremely difficult to predict how someone will perpetrate a terrorist act. Nevertheless, we believe that certain biological agents are at higher relative risk than others of being targeted for use as a biological weapon. We argue that an agent intended to yield high consequences is more attractive to terrorists when it is easy to acquire, develop, and disseminate than when it is not. Also, if terrorists had two agents with similar technical challenges, we believe that they would choose the agent that could cause higher consequences if used maliciously. Therefore, the assessment of a given agent's risk of being disseminated as a terrorist weapon should focus on two principal factors: (1) the ease or difficulty of using the agent maliciously, or its "task complexity," and (2) the consequences that would result if the agent were disseminated maliciously, or its "consequences of use." The agent's risk of malicious use would be a function of both its task complexity and its consequence of use.[40]

Ultimately, an agent-based risk assessment would allow policymakers to identify and address the most salient aspect of bioterrorism prevention: high-risk agents. The assessment would also provide benefits as the U.S. begins to work with the international community.[35] While countries may choose to prioritize agents differently for a variety of reasons—such as whether a given agent is endemic to the region—the existence of a common methodology focused on relative risk would speed implementation among countries with varied operating environments, political concerns, and national resources. This methodology would also allow U.S. policymakers and the global community to assess newly emerging biological agents, such as SARS and highly pathogenic avian influenza, evaluating whether such agents constitute a high risk of malicious use.

Facility and Transport Biosafety and Biosecurity

Recently, the U.S. and the international community have expressed concern about the vulnerability of biological agents in legitimate bioscience facilities or transport carriers, urging that measures be developed and implemented to help reduce the risk of theft and misuse of these agents worldwide. Since 2003, U.S. regulations have required select agent facilities and individuals to adhere to specific laboratory biosafety and biosecurity procedures designed to maintain oversight and control of those materials.[36] Many nations are in the process of developing their own biosafety and biosecurity regulations. The World Health Organization (WHO) *Laboratory Biosafety Manual 3rd Edition* represents the current international guidelines for biosafety,[41] and WHO has just published its first laboratory biosecurity guidelines.[42]

Dangerous pathogens and toxins continue to be used and stored for legitimate research purposes in hundreds if not thousands of legitimate bioscience facilities worldwide. Within a global materials management program, laboratory biosafety and biosecurity should aim to protect *high-risk agents*—not all or even most biological agents—against accidental exposure or release as well as intentional theft and misuse. This would be a particularly important consideration in the international community, where funding for biosafety and biosecurity often must compete for resources used to combat natural outbreaks of highly infectious disease. A focus on high-risk agents also would minimize the extent to which these safety and security systems would constrain legitimate and life-saving research activities. The emerging laboratory biosecurity community has articulated that internal procedural controls, especially personnel management, are most important for protecting biological materials against theft and misuse.[43–45] Thus, it is important for the U.S. and international policy communities to understand that effective laboratory biosecurity does not depend on an expensive, high-technology security system but on a management process that ensures responsibility and oversight of high-risk agents. These management techniques are not difficult to teach and implement at relatively low cost.

A global biological materials management program should focus on developing laboratory biosecurity implementation guidelines that would be appropriate for the international community, creating regional professional biosafety and biosecurity organizations to promote these concepts, assisting countries in developing national laboratory biosafety and biosecurity guidelines and/or legislation, and supporting technical implementation at laboratories throughout the world in most need of risk reduction. There are important precedents in related fields that demonstrate the value of such an approach. In 1975, the International Atomic Energy Agency (IAEA) published guidelines for the physical protection of nuclear material, and in 2001 the IAEA published a code for the safety and security of radioactive sources. Subsequent revisions of these documents have become reference standards globally, and security of these nuclear and radioactive materials has been significantly improved around the world as a result.[46–48] And perhaps professional organizations such as the American Biological Safety Association [www.absa.org] can serve the role for laboratory biosecurity that the Institute of Nuclear Materials Management [www.inmm.org] has become for nuclear and radiological security.

In contrast to the concern over the security of dangerous pathogens and toxins in laboratories, limited attention has been given to the security of these materials in transport systems. High-risk agents are often transported locally, nationally, and internationally for legitimate diagnostic, medical, and research purposes, and thus they are vulnerable to theft in the transport system as well as in laboratories. Yet, internationally, the emphasis has been on ensuring the *safe* transport of biological materials; no international transport regulations exist to achieve the *secure* transport of dangerous agents.

A global biological materials management program should promote international transport security practices based on chain of custody procedures—a record of those in possession of the material en route—and verification of legitimate need to use high-risk agents. Such relatively simple procedures, which would not be expensive or difficult to implement, would ensure personal accountability for specific packages throughout transport, culminating in confirmation on delivery. A global biological materials management program should aid interested countries in developing and implementing suitable distribution and transport security legislation, policies, and practices, as well as aim to harmonize similar regulations at the international level.

Pathogen Surveillance and Outbreak Control

High-risk agents can be found in the natural environment, where they cause outbreaks of infectious disease. Over time new dynamic reservoirs of high-risk agents continue to arise. These agents are distributed among a variety of sources, including infected humans and animals, soil, water, and insect vectors, as well as diagnostic and research facilities. Samples from outbreak sites must be collected and analyzed and victims diagnosed and treated. In order to reduce the opportunity for those with malicious intent to acquire high-risk agents from publicized outbreaks, the sites of the outbreaks and the diagnostic and clinical pathways should be controlled.

The possibility that high-risk agents resulting from disease outbreaks may be targeted for use in bioterrorism is no longer a matter of speculation. In 1992, members of the Japanese cult Aum Shinrikyo traveled to an Ebola outbreak in the former Zaire to try to acquire a sample of that virus so that they could develop an Ebola biological weapon. Fortunately, their efforts were unsuccessful, even though isolating an agent from nature when it is widespread during an outbreak would be technically less challenging than isolating it in a nonoutbreak situation.[49]

The recent threat of an avian influenza pandemic has prompted the international community to strengthen disease surveillance networks. Yet, as the continuous spread of highly pathogenic avian influenza demonstrates, international disease surveillance remains weak, and in some countries outbreak control measures are inadequate.[50–52] Moreover, the objective of most international disease surveillance and outbreak control initiatives is limited to strengthening public or animal health—and, in many cases, only to advancing infectious disease research. Arguably, the natural evolution and inadequate control of some highly infectious diseases increases the bioterrorism threat. Foot-and-mouth disease (FMD), the most contagious animal disease known, is now endemic across most of East Asia, South Asia, the Middle East, Central and Eastern Africa, and parts of Latin America. Besides the dramatic spread of this disease over the past decade, FMD epidemics appear to be occurring with increasing frequency.[53,54] And yet the FMD virus, which is relatively easy to isolate from a large-scale natural outbreak, has been associated with past biological weapons programs and identified as a potentially effective bioterror agent.[55,56]

Fortunately, WHO and the Food and Agriculture Organization have many infectious disease systems and initiatives in place throughout the world. A global biological materials management program could concentrate on augmenting systems that are specific to high-risk agents. In addition to identifying where high-risk agents exist in the environment, pathogen surveillance and outbreak control should also aim to detect potential bioterrorism testing programs, prevent the natural expansion of high-risk agents, and reduce terrorist access to large-scale natural outbreaks of this potential source material. Strengthening pathogen surveillance and control efforts internationally would not only enhance public and agricultural health, thus reducing the threat of infectious disease in general, but it also would limit the amount of high-risk agents stored and used in bioscience laboratories. Improved infectious disease detection and control will reduce the need to isolate, transport, store, and work with high-risk agents in laboratories.

Implementing improved pathogen surveillance and outbreak control will require close collaboration among health-related agencies and practitioners at local, national, regional, and international levels. Rather than search for and rely on expensive, high-technology solutions, the U.S. and the international community should develop and implement straightforward procedures that are easy to teach and put into practice. Basic molecular diagnostics can significantly increase the speed and efficacy of traditional diagnostic methods. Simple web interfaces, which can be enhanced with widely available Geographic Information System (GIS) data, can be developed to rapidly communicate diagnostic test data and results. Once an outbreak is identified, and if it is thought to be limited to a specific location, the site should be quarantined to prevent movement into and out of the area. Samples collected and transported from the outbreak site to diagnostic facilities should be transported by safe and secure methods to minimize the risk of accidental release or theft of the agent while in transit. Measures should be taken to safeguard animal carcasses so that disposal and sanitation measures are adequate and subject to inspection to ensure that all material has been removed and thoroughly decontaminated.

Conclusion

For the United States to successfully implement a comprehensive global biological materials management program, a multidimensional strategy must be employed that capitalizes on existing bilateral, regional, and multilateral partnerships. Bilateral engagement in regions simultaneously experiencing booming biotechnology, frequent infectious disease outbreaks, and terrorist activity should be given priority. While many countries fit one or more of these criteria, the conjunction is most noticeable in South, East, and Southeast Asia as well as the Middle East.

Many countries in these regions have already expressed an interest in protecting high-risk biological materials and have sought technical assistance on laboratory biosafety and biosecurity. Singapore has adopted its own "select agent" legislation, the Biological Agents and Toxins Act. Japan is now in the process of amending its Infectious Disease Law to regulate possession and production of pathogens. The newly formed Asia-Pacific Biosafety Association [www.a-pba.org] seeks to increase awareness and provide a forum for technical exchange on both biosafety and biosecurity. At the first annual A-PBA meeting in March 2006, Malaysia described the roles and responsibilities of its newly formed National Biosafety Committee, which is responsible for drafting a cabinet-level National Laboratory Biosafety and Biosecurity Policy. In May 2006, the U.S. and India jointly sponsored the first technical workshop in India on laboratory biosafety and biosecurity issues. The U.S. and Jordan held a similar workshop for 15 Middle Eastern countries in April 2006, and WHO held another regional workshop on this topic in Iran in October 2006

[www.biosecurity.sandia.gov]. The U.S. Department of State recently created a Biosecurity Engagement Program [www.bepstate.net] to promote these concepts globally. But these initiatives are only preliminary and need to be supported with long-term programs and resources.

Such biological threat reduction would also help strengthen international bioscience. In general, the most dangerous infectious diseases today are tropical diseases. And the overwhelming majority of the countries in the tropics that suffer from these diseases are developing countries that generally lack the resources, knowledge, and ability to adequately detect, respond to, and control these diseases—let alone to work safely and securely with the causative pathogens. Thus, global biological materials management should focus on engaging the legitimate international bioscience community—especially in the developing world—and demonstrating the value of adopting practices to manage high-risk biological materials safely and securely.

Improving the management of international bioscience would not only reduce the opportunity for someone to exploit a legitimate laboratory to intentionally disseminate disease, but would also facilitate the integration of biomedical research and science across the developing and developed world. Collaborative biomedical and bioscience research would increase, enhancing knowledge about emerging tropical diseases and strengthening the developing world's ability to control those endemic diseases. This integration of diverse bioscience communities may ultimately be the most effective form of threat reduction.

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REFERENCES

1. Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology, National Research Council. *Biotechnology Research in an Age of Terrorism: Confronting the Dual Use Dilemma.* Washington, DC: National Academy of Sciences; 2003.
2. Nixdorff K, Bender W. Biotechnology, ethics of research, and potential military spin-off. *INESAP Bulletin* 2002;19. Available at: http://www.inesap.org/bulletin19/bul19art05.htm. Accessed April 18, 2007.
3. Kwik G, Fitzgerald J, Inglesby TV, O'Toole T. Biosecurity: responsible stewardship of bioscience in an age of catastrophic terrorism. *Biosecur Bioterror* 2003;1(1):27–35.
4. Salerno RM, Gaudioso J, Frerichs RL, Estes D. A BW risk assessment: historical and technical perspectives. *Nonproliferation Review* 2004;11(3).
5. Office of Transnational Issues. *The Darker Bioweapons Future.* Washington, DC: Central Intelligence Agency; November 3, 2003. Available at: http://www.fas.org/irp/cia/product/bw1103.pdf. Accessed April 18, 2007.
6. *Mapping the Global Future.* Report of the National Intelligence Council's 2020 Project. Washington, DC: National Intelligence Council; 2004. Available at: http://www.dni.gov/nic/NIC_globaltrend2020.html. Accessed April 18, 2007.
7. Commission on the Intelligence Capabilities of the United States Regarding Weapons of Mass Destruction. *Report to the President of the United States.* Washington, DC: Commission on the Intelligence Capabilities of the United States; 2005. Available at: http://www.whitehouse.gov/wmd/. Accessed April 18, 2007.
8. The White House. *Biodefense for the 21st Century.* Washington, DC: White House; 2004. Available at: http://www.whitehouse.gov/homeland/20040430.html. Accessed April 18, 2007.
9. UN Security Council Resolution 1540 (2004). New York: United Nations; April 28, 2004. Available at: http://www.state.gov/documents/organization/32097.pdf. Accessed April 18, 2007.
10. *Appeal on Biotechnology, Weapons and Humanity.* Geneva: International Committee of the Red Cross; 2002. Available at: http://www.icrc.org/Web/eng/siteeng0.nsf/htmlall/5EAMTT. Accessed April 18, 2007.
11. Preventing Bioterrorism: The 1st Interpol Global Conference to strengthen law enforcement preparedness and develop effective police training. Paris: Interpol; 2005. See: http://www.interpol.int/Public/BioTerrorism/Conferences/1stGlobalConference.asp. Accessed April 18, 2007.
12. International Futures Programme (IFP). *Program on Biosecurity.* Paris: Organization for Economic Cooperation and Development; 2004. Available at: http://www.biosecuritycodes.org/about.htm. Accessed April 18, 2007.
13. National Science Advisory Board for Biosecurity. 2005. See: http://www.biosecurityboard.gov/index.asp. Accessed April 18, 2007.
14. Committee on Advances in Technology and the Prevention of Their Application to Next Generation Biowarfare Threats, National Research Council. *Globalization, Biosecurity, and the Future of the Life Sciences.* Washington, DC: National Academy Press; 2006.
15. Somerville MA, Atlas RM. Ethics: a weapon to counter bioterrorism. *Science* 25 March 2005;307:1881–1882.
16. Steinbruner J, Harris ED. Controlling dangerous pathogens. *Issues Sci Technol* 9 April 2003. Available at: http://www.issues.org/19.3/steinbruner.htm. Accessed April 18, 2007.
17. Steinbruner J, Harris ED, Gallagher N, Okutani S. *Controlling Dangerous Pathogens: A Prototype Protective Oversight System.* College Park, Md: Center for International and Security Studies at Maryland; 2005. Available at: http://www.cissm.umd.edu/papers/files/pathogens_project_monograph.pdf. Accessed April 18, 2007.

18. Jackson RJ, Ramsay AJ, Christensen CD, Beaton S, Hall DF, Ramshaw IA. Expression of mouse interleukin-4 by a recombinant ectromelia virus suppresses cytolytic lymphocyte responses and overcomes genetic resistance to mousepox. *J Virol* 2001;75(3):1205–1210.
19. Cello J, Paul AV, Wimmer E. Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template. *Science* 2002;297(5583):1016–1018.
20. Smith HO, Hutchison CA 3rd, Pfannkoch C, Venter JC. Generating a synthetic genome by whole genome assembly: phi X174 bacteriophage from synthetic oligonucleotides. *Proc Natl Acad Sci U S A* 2003;100(26):15440–15445.
21. Tumpey TM, Basler CF, Aguilar PV, et al. Characterization of the reconstructed 1918 Spanish influenza pandemic virus. *Science* 2005;310(5745):77–80.
22. Atlas RM, Reppy J. Globalizing biosecurity. *Biosecur Bioterror* 2005;3(1):51–60.
23. Barletta M, Sands A, Tucker JB. Keeping track of anthrax: the case for a pathogen security convention. *Bull At Sci* 2002;58(3).
24. Kellman B. *Draft Convention on the Prohibition and Prevention of Biological Terrorism 2002*. Prepared for the Workshop on Biological Terrorism—An International Criminal Law Approach; April 29, 2002. Chicago: International Human Rights Law Institute, DePaul University; 2002. Available at: http://www.law.edpaul.edu/institutes_centers/ihrli/_downloads/draft_convention.pdf. Accessed April 18, 2007.
25. Public consultation on the proposed Biological Agents and Toxins Act. Presented at Regional Emerging Disease Intervention (REDI) Centre Meeting on International Laboratory Biosafety and Biosecurity; April 7–8, 2005; Ministry of Health, Singapore.
26. Donahue LK. Censoring science won't make us any safer. *Washington Post* June 26, 2005.
27. Scheuer M. *Through Our Enemies' Eyes: Osama bin Laden, Radical Islam, and the Future of America*. Dulles, Va: Brassey's; 2002.
28. Petro JB, Relman DA. Understanding threats to scientific openness. *Science* December 12, 2003;302:1898.
29. Anisimov AP, Lindler LE, Pier GB. Intraspecific diversity of Yersinia pestis. *Clin Microbiol Rev* 2004;17(2):434–464.
30. World Health Organization. Human plague in 2002 and 2003. *Wkly Epidemiol Rec* August 13, 2004;79(33):301–308. Available at: http://www.who.int/wer/2004/en/wer7933.pdf. Accessed April 19, 2007.
31. Jackson RJ, Ramsay AJ, Christensen CD, Beaton S, Hall DF, Ramshaw IA. Expression of mouse interleukin-4 by a recombinant ectromelia virus suppresses cytolytic lymphocyte responses and overcomes genetic resistance to mousepox. *J Virol* Feb 2001;75(3):1205–1210.
32. Vogel KM. Pathogen proliferation: threats from the former Soviet bioweapons complex. *Politics Life Sciences* 2000;19(1):3–16.
33. Cook MS, Woolf AF. *Preventing Proliferation of Biological Weapons: U.S. Assistance to the Former Soviet States*. Washington, DC: Congressional Research Service; April 10, 2002. Available at: http://fpc.state.gov/documents/organization/9658.pdf. Accessed April 19, 2007.
34. Luongo KN, Averre D, Della Ratta R, Martellini M. Building a forward line of defense: securing former Soviet biological weapons. *Arms Control Today* 2004;34(6).
35. Petro JB, Carus WS. Biological threat characterization research: a critical component of national biodefense. *Biosecur Bioterror* 2005;3(4):295–308.
36. Code of Federal Regulations, Title 42, Parts 72 and 73. Code of Federal Regulations, Title 7 Part 331. Code of Federal Regulations, Title 9, Part 121.
37. Rotz LD, Khan AS, Lillibridge SR, Ostroff SM, Hughes JM. Public health assessment of potential biological terrorism agents. *Emerg Infect Dis* 2002;8(2):225–230.
38. Casadevall A, Pirofski LA. The weapon potential of a microbe. *Trends Microbiol* 2004;12(6):259–263.
39. Gaudioso J, Salerno RM. Science and government. Biosecurity and research: minimizing adverse impacts. *Science* April 30, 2004;304(5671):687.
40. Gaudioso J, Salerno RM, Barnett N. Developing a risk assessment and management approach to laboratory biosecurity. *Applied Biosafety* 2006;11(1):24–31.
41. World Health Organization. *Laboratory Biosafety Manual*. 3rd ed. Geneva: World Health Organization; 2004. Available at: http://www.paho.org/English/AD/THS/EV/LAB-Biosafety_OMS.pdf. Accessed April 19, 2007.
42. World Health Organization. *Biorisk Management: Laboratory Biosecurity Guidance*. Geneva: World Health Organization; 2006. Available at: http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_EPR_2006_6/en/index.html. Accessed April 19, 2007.
43. Tucker JB. *Biosecurity: Limiting Terrorist Access to Deadly Pathogens. Peaceworks No. 52*. Washington, DC: United States Institute of Peace; 2003. Available at: http://www.usip.org/pubs/peaceworks/pwks52.pdf. Accessed April 19, 2007.
44. Salerno RM, Estes D. Biosecurity: protecting high consequence pathogens and toxins against theft and diversion. In: Pilch R, Zilinskas R, eds. *Encyclopedia of Bioterrorism Defense*. Hoboken, NJ: Wiley; 2005.
45. Rao V, Eilers A, Mancini C. Select agents diagnostic test reporting requirements—exemptions and implications to biosecurity. *Applied Biosafety* 2006;11(4):215–221.
46. *The Physical Protection of Nuclear Material and Nuclear Facilities*. INFCIRC/225/Rev.4. Vienna: International Atomic Energy Agency; 1999. Available at: http://www.iaea.org/Publications/Documents/Infcircs/1999/infcirc225r4c//rev4_content.html. Accessed April 19, 2007.
47. *Code of Conduct on the Safety and Security of Radioactive Sources*. Vienna: International Atomic Energy Agency; 2004. Available at: http://www-ns.iaea.org/tech-areas/radiation-safety/code-of-conduct.htm. Accessed April 19, 2007.
48. *Review of the Implementation of the IAEA Nuclear Security Plan of Activities: 2002-2005*. Vienna: International Atomic Energy Agency, 2006.
49. Christopher GW, Cieslak TJ, Pavlin JA, Eitzen EM Jr. Biological warfare: a historical perspective. In: Lederberg J, ed. *Biological Weapons: Limiting the Threat*. Cambridge, Mass: MIT Press; 1999: Chap. 3.
50. Kuiken T, Leighton FA, Fouchier RAM, et al. Pathogen surveillance in animals. *Science* September 9, 2005;309:1680–1681.
51. Jebara KB. Surveillance, detection and response: managing

emerging diseases at national and international levels. *Rev Sci Tech* 2004;23(2):709–715.
52. Butler D. Disease surveillance needs a revolution. *Nature* March 2, 2006;440:6–7.
53. *Global Livestock Production and Health Atlas.* Rome, Italy: Food and Agriculture Organization; 2004. Available at: http://www.fao.org/ag/aga/glipha/index.jsp. Accessed April 19, 2007.
54. Risk assessment on foot and mouth disease. *EFSA Journal* 2006;313:1–34. Available at: http://www.efsa.europa.eu/etc/medialib/efsa/science/ahaw/ahaw_opinions/1357.Par.0001.File.dat/aha w_op_ej313_fmd_en1.pdf. Accessed April 19, 2007.
55. Wheelis M, Casagrande R, Madden LV. Biological attack on agriculture: low-tech, high-impact bioterrorism. *BioScience* 2002;52(7):569–576.
56. Cupp OS, Walker DE II, Hillison J. Agroterrorism in the U.S.: key security challenges for the 21st century. *Biosecur Bioterror* 2004;2(2):97–105.

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